CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202276Orig1s000

SUMMARY REVIEW

Acting Deputy Division Director Summary Review

Date	April 26, 2012
From	Audrey Gassman, MD
NDA #	202276
Applicant name	VIVUS, Inc.
Date of receipt of original submission	June 29, 2011
PDUFA goal date	April 29, 2012
Proprietary name/established name	Stendra/avanafil
Dosage Form/strength	Tablet/50mg, 100 mg and 200 mg
Proposed Indication	Treatment of erectile dysfunction
Action	Approval

Material reviewed/consulted	Names of discipline reviewers
CDTL Review	Mark Hirsch, MD
Medical Officer Review	Guodong Fang, MD
Statistical Review	Jia Guo, PhD Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Yangmee Shin, PhD Lynnda Reid, PhD Abigail Jacobs, PhD
Clinical Pharmacology Review	LaiMing Lee, PhD Myong-Jin Kim, PhD
ONDQA Review	Hamid Shafiei, PhD Moo Jhong Rhee, PhD Terrance Ocheltree, PhD, RPh
DMEPA	Zachary Oleszczuk, PharmD
DMPP	Shawna Hutchins, MPH, BSN, RN Melissa Hulett, RN, BSN, MSBA LaShawn Griffiths, RN, MSHS-PH, BSN
OPDP	Jessica Cleck Derenick, PhD Jina Kwak, PharmD
OSI	Roy Blay, PhD Janice Pohlman, MD, MPH Tejashri Purohit-Sheth, MD
SEALD	Jeannie Delasko, RN, MS Laurie Burke RPh, MPH

CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
DMEPA=Division of Medication Error Prevention and Analysis
ONDQA – Office of new Drug Quality Assessment
DMPP=Division of Medical Policy Programs
OPDP= Office of Prescription Drug Promotion
DPP – Division of Professional Promotion
DDTCP – Division of Direct-to-Consumer Promotion
OSI=Office of Scientific Investigations
SEALD = Study Endpoints and Labeling Development Team

1. **Introduction**
2. **Background**
3. **CMC**
4. **Nonclinical Pharmacology/Toxicology**
5. **Clinical Pharmacology**
6. **Clinical Microbiology**
7. **Efficacy/Statistics**
8. **Safety**
9. **Advisory Committee Meeting**
10. **Pediatrics**
11. **Other Relevant Regulatory Issues**
12. **Labeling**
13. **Decision/Action/Risk Benefit Assessment**

1. Introduction

VIVUS, Inc. submitted an NDA (202-276) containing a proposed new phosphodiesterase type-5 (PDE-5) inhibitor in a tablet formulation. The active ingredient in this new PDE-5 inhibitor is avanafil (trade name Stendra). Avanafil increases penile blood flow and improves erection in response to sexual stimulation. Four other PDE-5 inhibitors are currently approved for treatment of erectile dysfunction (ED) including: sildenafil (Viagra – approved March, 1998), tadalafil (Cialis – approved November, 2003), vardenafil (Levitra – approved August 2003) and Staxyn (vardenafil in an oral disintegrating tablet – approved June 2010). The proposed indication for avanafil is "treatment of erectile dysfunction," an indication identical to the other currently approved PDE-5 inhibitors.

Stendra (avanafil) is a solid, oval, pale yellow immediate-release (IR) oral tablet and is intended to be used on an as needed basis. The proposed dosing regimen is one 100 mg tablet taken 30 minutes prior to initiation of sexual activity and no more than once daily. The dose may be increased to 200 mg or decreased to 50 mg based on efficacy and/or tolerability. The Applicant is seeking approval for 50 mg, 100 mg, and 200 mg tablets. To support approval of this NDA, the Applicant conducted a total of 23 clinical studies that included: 17 phase I studies, 3 phase II studies, 2 phase III studies and an open-label long-term extension study. The primary efficacy outcome for the phase III studies was measured by the IPSS, an endpoint evaluated in the other PDE 5 inhibitor products approved for the treatment of ED.

All PDE 5 inhibitor products including avanafil, are vasodilators and have the potential effect of lowering systemic blood pressure. Safety issues of concern that were evaluated by review teams during the development program for Stendra included the potential of causing clinically significant lowering of blood pressure (hypotension). Other safety issues of concern for PDE 5 inhibitors that were also evaluated in the Stendra subject database included effects on vision, possible cardiac risks and interaction of Stendra with concomitant drugs such as organic nitrates, antihypertensives, alpha blockers and alcohol.

2. Background

The Applicant initiated discussions with the Division of Reproductive and Urologic Products (DRUP) on the development plan for Stendra (avanafil/TA-1790) at a pre-IND meeting held on November 7, 2001. IND 51,235 (avanafil for the treatment of ED) was opened on November 30, 2001, with a pilot, single dose, dose escalating study (TA-01) evaluating avanafil 50, 100, and 200 mg. Clinical trials of avanafil were subsequently conducted that evaluated approximately 450 subjects and included doses from 12.5 mg to 800 mg.

On November 2, 2005, an End of Phase 2 (EOP2) meeting was held between the Applicant and DRUP to discuss Phase 3 development of avanafil. The Applicant provided protocol synopses and proposed to conduct two pivotal Phase 3 studies (one in the general ED population and one in diabetics only), one Phase 3 study in men with ED who had undergone radical prostatectomy, and one 12-month open label safety extension study. The Division provided comments and recommendations on the Applicant's proposed development plan at this 2005 meeting, which included the following: "The number of patients to be studied in Phase 3 is sufficient and the primary endpoints and duration of the double-blind treatment are acceptable. Two phase 3 studies in the "general" ED group should be performed…Extension safety trials with at least 100 patients treated for 1 year will be required."

During the Phase 3 clinical trial development, the Division responded with advice regarding the Applicant's proposed "pivotal" clinical trials: TA-301 (in the general ED population), TA-302 (in diabetic men) and TA-303 (in radical prostatectomy patients) through special protocol assessments (SPAs). The Division also reviewed the protocol for TA-314 (long-term extension study) and sent an advice letter on April 20, 2009.

On October 20, 2010, a preNDA meeting was held between DRUP and the Applicant. At that meeting, the Division agreed that the patient exposure in the avanafil program was sufficient to support approval. DRUP also acknowledged that Study TA-303 in subjects with ED following radical prostatectomy was still ongoing because of slow enrollment. and concurred that the NDA could be submitted without this study. Safety data from the ongoing Study TA-303 were incorporated into the 120-Day Safety Update.

NDA 202-276 was submitted to DRUP on June 29, 2011, and contained results from a total of 23 clinical studies to support the efficacy and safety of avanafil. The two phase 3 studies (TA-301 and TA-302) were reviewed as pivotal efficacy studies. The other studies were considered supportive safety studies and included the following: 3 phase 2 studies (TA-01, TA-03 and TA-05), the single open-label extension study (TA-314) and 17 phase 1 studies that evaluated a variety of pharmacokinetic and pharmacodynamic issues including a thorough QT study (TA-140), a single dose study on the effects on sperm (TAS-021) or vision (HP-01 and TA-016).

3. ONDQA

Stendra tablets contain [redacted] avanafil API as the active ingredient, and mannitol [redacted] fumaric acid [redacted] hydroxypropylcellulose [redacted] low substituted hydroxypropylcellulose [redacted] calcium carbonate [redacted] magnesium stearate [redacted] and yellow ferric oxide [redacted] as excipients. All excipients used in the manufacture of this drug product are compendial excipients. All strengths of avanafil tablets are packaged as 30 tablets or 100 tablets in white HDPE bottles enclosed with white child-resistant screw caps. Stendra tablets are also packaged in 3-tablet blister cards. The blister card packaging configuration is intended only for use as physician samples.

The Chemistry Review (ONDQA) team made the following initial recommendation in their review dated March 1, 2012, "The applicant of this NDA has not provided sufficient information to assure identity, strength, purity, and quality of the drug product, TRADENAME (avanafil) tablets. However, the Office of Compliance has not made an overall "Acceptable" recommendation regarding the facilities involved in this NDA. Also label/labeling issues identified have not been satisfactorily resolved. Therefore, from the ONDQA perspective, this NDA is not recommended for approval in its present form, per 21 CFR 314.125(b)(1),(6) & (13)."

In an addendum to the October, 2011, ONDQA review, finalized on April 17, 2012, the ONDQA review team stated that, "The applicant has submitted an amendment on March 19, 2012 that includes a master batch record that fully reflects the proposed set points for the critical process parameters identified and recommended for the large scale commercial manufacturing of the avanafil tablets. The CMC label/labeling issues have been resolved via the amendments dated March 13, 2012 and April 11, 2012. This drug product is intended for marketing in the United States under the trade name "Stendra" (see the Attachment -2). The Office of Compliance has also made an overall recommendation of "Acceptable" for the facilities involved in this NDA on April 17, 2012 (see the Attachment-1). Therefore, this NDA is now recommended for approval from the ONDQA perspective."

In the tertiary ONDQA review memo signed on April 17, 2012, the ONDQA Division Director stated, "I concur with the "Approval" recommendation from an ONDQA perspective and the absence of ONDQA related post marketing commitments."

Comment: There are no outstanding CMC issues. I concur with the "Approval" recommendation of the ONDQA review team.

4. Nonclinical Pharmacology/Toxicology

Nonclinical data submitted to support approval of avanafil included general and safety pharmacology and pharmacokinetic studies, including a single-dose phototoxicity study. The pharmacology/toxicology review team stated in their review dated March 21, 2012, that, "From a Pharmacology/Toxicology perspective, the nonclinical data submitted

support the approval of avanafil for the treatment of erectile dysfunction at the proposed doses."

The pharmacology/toxicology supervisor stated in her review (dated March 26, 2012) that, "I concur with the primary nonclinical reviewer, Dr. Yangmee Shin, that nonclinical data support approval of avanafil at doses up to 200 mg, to be used on an as needed basis for the treatment of erectile dysfunction." On March 26, 2012, the Associate Director for pharmacology/toxicology also finalized a brief memo stating her concurrence with the primary pharmacology/toxicology reviewer and supervisor.

Comment: I concur with the approval recommendation of the pharmacology/toxicology review team from a pharmacology/toxicology perspective. The pharmacology/toxicology review team recommended that a statement in labeling indicating that, "that the effect of avanafil on human spermatogenesis is unknown. However, because of the lack of clinical information with multiple dose use of avanafil in humans on sperm, a post-marketing clinical trial will be requested to further evaluate potential effects on spermatogenesis in men following repeat-dose administration. This trial will be a postmarketing requirement.

5. Clinical Pharmacology

The Clinical Pharmacology review team evaluated data from the clinical studies that contained relevant Clinical Pharmacology data and presented their findings in two reviews (one review of individual study reports and the other a question-based review and executive summary, both dated March 9, 2012). The proposed dosing regimen for avanafil is one 100 mg tablet 30 minutes prior to initiation of sexual activity and no more than once daily. The dose may be increased to 200 mg daily or decreased to 50 mg based on efficacy and/or tolerability. The Applicant sought approval of all three tablet strengths (50 mg, 100 mg and 200 mg).

Although initial phase 1 studies were performed with an avanafil immediate release formulation (Formulation I), (b) (4) (Formulation II) was used in the phase 3 program, as well as in the majority of the Clinical Pharmacology studies. Formulation II was designated as the "to-be-marketed" formulation of avanafil. Formulation II showed biphasic elimination with a half-life of 5 hours (range 4.5 to 6.4 hrs) reported following a single dose of avanafil 50 to 200 mg in most Clinical Pharmacology studies. This half-life was mostly based on second elimination phase. Therefore, the terminal elimination half-life was determined to be approximately 5 hrs. Time to maximum concentration (Cmax) was reached 0.5 to 0.75 hrs after ingestion in healthy young men given a single 200 mg dose of avanafil, Formulation II.

Other Clinical Pharmacology findings included:

- Based on the phase 3 clinical trials of Stendra, dosing was done on-demand without regard to food and therefore Stendra will be labeled for dosing irrespective of food intake.

- Based on phase 1 clinical trials of Stendra, the following dose modification recommendations were made by the Clinical Pharmacology review team:
    - Renal impairment: No dose adjustment for mild or moderate renal impairment.
    - Not recommended for use in patients with severe renal disease or on renal dialysis.
    - Hepatic impairment: No dose adjustment for mild or moderate hepatic impairment.
    - Not recommended for use in patients with severe hepatic impairment.
    - Use with potent CYP3A4 inhibitors: Not recommended
    - Use with any form of organic nitrates: Not recommended

As the target population of men with ED is likely to be older and potentially prone to having hypertension and benign prostate hyperplasia (BPH), the Applicant conducted drug-drug interaction studies on the concomitant use of Stendra and drugs used to treat these conditions (alpha-adrenergic blockers, angiotensin converting enzyme inhibitors and calcium channel blockers). The Applicant also evaluated the effect of Stendra co-administered with warfarin.

Comment: Drug-drug interactions studies were reviewed by the Clinical Pharmacology team. The Clinical Pharmacology team concluded that the three dosage strengths (50 mg, 100 mg and 200 mg) and dosage regime without regard to food intake, proposed by the Applicant, was acceptable. In addition, results of extrinsic and intrinsic factor studies (such as alcohol intake and hepatic and renal impairment), and drug-drug interaction studies will be labeled where appropriate.

On November 30, 2011, the Interdisciplinary Review Team (IRT) for QT Studies provided a consult regarding the Applicant's thorough QT study (TA-140) and made the following recommendation, "The upper bound of 90%CI for ΔΔQTcF exceeds 10 ms at one time point for the supratherapeutic dose (800 mg). However, after accounting for the effect of known intrinsic and extrinsic factors, neither the therapeutic doses of avanafil (100 or 200 mg), nor the proposed adjusted avanafil dose when coadministered with a potent CYP3A4 inhibitor is expected to cause > 10 ms increase in QT, the threshold for regulatory concern."

Comment: I concur with the IRT review team that no QT signal was identified for avanafil.

The Clinical Pharmacology review team made the following recommendation in their review dated March 9, 2012, that, "The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed NDA 202276 for avanafil 50 mg, 100 mg, and 200 mg oral tablets submitted to the Agency on June 29, 2011. We have found this NDA acceptable from a Clinical Pharmacology perspective provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert."

No postmarketing commitments or requirements were recommended by the Clinical Pharmacology review team.

Comment: I concur with the approval recommendation of the Clinical Pharmacology review team. There are no outstanding Clinical Pharmacology issues.

6. Clinical Microbiology

No clinical microbiological issues were identified for this application and the Applicant's proposed testing for microbiological attributes was determined to be acceptable to the Microbiology Staff (See Attachment II in the ONDQA review dated March 1, 2012).

7. Efficacy/Statistics

The pivotal studies for Stendra (TA-301 and TA-302) provided evidence for the efficacy of Stendra for the treatment of erectile dysfunction. The design of the two clinical trials was identical, with the exception that the population studied in TA-302 was diabetic. The two pivotal trials were multi-center, randomized, double-blind, parallel trials evaluating the on demand use of different doses of avanafil as compared to placebo. Of note, TA-301 studied three doses of Stendra (50 mg, 100 mg and 200 mg); TA-302 studied two doses (100 mg and 200 mg). The Applicant classified a third study as "pivotal" (TA-05), although this study was a phase 2 study.

Comment: Study TA-05 was a Phase 2 study that excluded subjects with severe ED and I concur with the clinical review team that this study should be considered supportive. Therefore, the focus of the review on efficacy will be on the two pivotal studies TA-301 and TA-302.

Inclusion – exclusion criteria for the pivotal phase 3 studies:

The main criteria for inclusion for the two phase 3 studies (TA-301 and TA-302) were adult men ($\geq$ 18 years of age) with mild to severe erectile dysfunction for at least 6 months as defined by the IIEF erectile function domain score.

Study TA-301 excluded subjects who were diabetic or had a prostatectomy for prostate cancer.

Study TA-302 enrolled subjects with documented type 1 or 2 diabetes.

Comment: Another phase 3 study, Study TA-304 enrolled subjects that had undergone a prostatectomy for prostate cancer. Study TA-304 was not completed prior to NDA submission and, therefore, data from this study were reviewed solely for safety purposes.

Study design for the pivotal phase 3 studies (TA-301 and TA-302):

For Studies TA-301 and TA-302, subjects who met the initial eligibility criteria entered the 4-week, non-treatment run-in period and recorded information on each of their attempts at sexual intercourse. At the end of the run-in period, subjects were eligible for randomization to treatment if they met the following criteria:

- Documented at least 4 attempts at sexual intercourse during the run-in period;
- Failed to maintain an erection of sufficient duration to have successful intercourse (as documented in the subject diary during the run-in period) for at least 50% of their attempts; and
- Had an International Index of Erectile Function – Erectile Domain (IIEF-EF) score of 5 to 25, inclusive.

Study drug was to be taken, approximately 30 minutes prior to intercourse, but not more than once in 24 hours. The placebo-controlled treatment period was 12 weeks. A Subject Diary was completed for each sexual encounter during this period.

In Study TA-301, subjects were randomized in a 1:1:1:1 ratio to one of the following treatments: placebo, avanafil 50 mg, avanafil 100 mg, or avanafil 200 mg.

In Study TA-302, subjects were randomized in a 1:1:1 ratio to one of the following treatment groups: placebo, avanafil 100 mg or avanafil 200 mg.

Randomization in Studies TA-301 and TA-302 was stratified using a computer-generated randomization system by disease severity as determined by IIEF erectile function domain scores (mild = IIEF score of 17 to 25; moderate = IIEF score of 11 to 16; severe = IIEF score ≤10) at the randomization visit. During the placebo-controlled treatment period for both studies, subjects were to take one dose of study drug approximately 30 minutes prior to the initiation of sexual activity. Subjects could take up to two doses of study drug per 24-hour period provided that the doses were separated by at least 12 hours. Subjects were requested to make at least 4 attempts at sexual activity per month.

Endpoints for the pivotal phase 3 studies:

Three co-primary efficacy endpoints were evaluated in the two pivotal phase 3 studies:

- International Index of Erectile Function – Erectile Domain (IIEF-ED). The IIEF is a validated instrument for evaluating erectile function. The Erectile Domain score is the total of the scores for six questions (Q1, Q2, Q3, Q4, Q5, and Q15). The IIEF was administered at Visit 2 (baseline) and at Visit 4 (week 12). Change from baseline to week 12 was the endpoint evaluated.
- Sexual Encounter Profile Question 2 (SEP2) "Were you able to insert your penis into your partner's vagina?" This question was answered in the Subject Diary for each sexual encounter during both the baseline period and the treatment period. The percentage of "Yes" responses was calculated for each period. The change in "Yes" percentage from the baseline period to the treatment period was the endpoint evaluated.
- Sexual Encounter Profile Question 3 (SEP3) "Did your erection last long enough for you to have successful intercourse?" This question was answered in the Subject Diary for each sexual encounter during both the baseline period and the treatment period. The percentage of "Yes" responses was calculated for each period. The change in "Yes" percentage from the baseline period to the treatment period was the endpoint evaluated.

The three co-primary endpoints were evaluated simultaneously and it was pre-specified that all three must show a change from the baseline to week 12 that is significant at the $p \leq 0.05$ level for an overall finding of efficacy for Stendra.

Demographics for the pivotal studies:

The table below summarizes the demographic and baseline characteristics of the ITT population for pivotal study TA-301.

Table 1: Study TA-301 – Demographics and baseline characteristics (ITT group)

	Placebo (N=162)	Avanafil 50 mg (N=161)	Avanafil 100 mg (N=161)	Avanafil 200 mg (N=161)	Total (N=646)
Age (years)					
N	162	161	161	162	646
Mean (SD)	55.4(11.13)	55.4(10.81)	56.5(10.32)	55.7(11.3)	55.7(10.89)
Min - Max	23-77	29-83	23-88	24-80	23-88
Age category n(%)					
< 50 years	52(32.1)	50(31.1)	46(28.6)	45(27.8)	193(29.9)
≥ 50 years and < 65 years	74(45.7)	81(50.3)	76(457.2)	78(48.1)	309(47.8)
≥ 65 years	36(22.2)	30(18.6)	39(24.2)	39(24.1)	144(22.3)
Race n (%)					
White	131(80.9)	135(83.9)	137(85.1)	150(92.6)	553(85.6)
Black	28(17.3)	25(15.5)	21(13.0)	11(6.8)	85(13.2)
Asian	2(1.2)	1(0.6)	2(1.2)	1(0.6)	6(0.9)
Multiple	1(0.6)	0	1(0.6)	0	2(0.3)

Body mass index (kg/m^2)					
N	162	161	161	162	646
Mean ± SD	90.2(16.58)	91.7(17.73)	91.3(15.26)	91.3(16.64)	91.1(16.80)
Erectile dysfunction severity n(%)					
Mild	57(35.2)	56(34.8)	56(34.8)	56(34.6)	225(34.8)
Moderate	52(32.1)	53(32.9)	52(32.3)	53(32.7)	210(32.5)
Severe	53(32.7)	52(32.2)	53(32.9)	53(32.7)	211(32.7)

*Table 1 adapted from Table 6.1.2.1 from the Medical Officer's review dated April 17, 2012.

For Study TA-302, a summary of the demographic and baseline information included:

- Mean age of subjects was 58.0
- Mean body mass index was 31.5 kg/m^2.
- Ethnicity was reported in the overall treatment group as: White (80.5%), Black (17.2%), Asian (1.5%), Multiple (0.5%) and Unknown (0.3%)
- Erectile dysfunction severity reported in the overall treatment group as: Mild (21.8%), Moderate (31.3%) and severe (46.9%).

In his April 17, 2012, review, the Medical Officer concluded that, "The demographic figures for Studies TA-301 and TA-302 show a largely White study population (approximately 12-15% Black); with mild, moderate and severe ED reported by approximately 1/3 of study subjects, respectively; and the age of about 75% of the study population was ≥ 50. All of these demographics are acceptable for the target indication."

Comment: I concur with the Medical Officer that the demographic and baseline data from these studies would encompass those in the target population for Stendra.

Subject Disposition for the pivotal phase 3 studies (TA-301 and TA-302):

For Study TA-301, 1509 subjects were initially enrolled, of which 646 were randomized to treatment after the run-in period. Of the 646 randomized subjects, 550 (85.1%) completed the study and 96 (14.9%) subjects discontinued from the study. The percentage of subjects who discontinued from the study was similar across the treatment groups. The most common reasons for discontinuation from Study TA-301 included protocol non-compliance (which also includes subjects who withdrew consent) (8.2%), loss to follow-up (3.4%), and adverse event (2.6%).

For Study TA-302, 1378 subjects were enrolled in the study and 390 subjects were assigned randomly to treatment. Of the 390 randomized subjects, 333 (85.4%) subjects completed the study and 57 (14.6%) subjects discontinued from the study. The percentage of subjects who discontinued from Study TA-302 was similar across the treatment groups. The reasons for discontinuation from the study included protocol non-compliance (9.2%, also includes subject withdrawal of consent), subject lost to follow-up (3.8%), adverse event (1.0%), and requirement for an excluded medical treatment (0.5%).

Comment: In his April 17, 2012, review, the Medical Officer reviewed the subject disposition and discontinuation rates and determined that the completion and discontinuation rate for adverse events were acceptable. I concur with this determination.

Study results for the pivotal studies (TA-301 and TA-302):

The statistical review for this NDA was based on the two double-blind phase 3 studies, TA-301 and TA-302. Study TA-301 was conducted in the general ED population, and study TA-302 was in diabetic male subjects. The primary efficacy variables were defined as follows:

- change in the percentage of sexual attempts between the run-in period and the 12-week treatment period in which the subject was able to maintain an erection of sufficient duration to have successful intercourse (subject diary question 5, also referred to as SEP3);
- change in the percentage of sexual attempts between the run-in period and the 12-week treatment period in which the subject was able to insert his penis into his partner's vagina (subject diary question 4, also referred to as SEP2);
- change in the IIEF erectile function domain score from baseline to end of the 12-week treatment period.

For both studies, the Applicant analyzed each of the three co-primary efficacy variables by an ANCOVA model with treatment and baseline erectile dysfunction severity category as factors and baseline value as the covariate. Least-squares (LS) means, corresponding standard errors, and p-values for the change in each primary efficacy variable were presented by treatment group. For each treatment comparison of interest, the difference in LS means, corresponding standard error, two-sided 95% confidence interval, and two-sided p-value were derived from the ANCOVA model. All three co-primary endpoints must be significant at the $p \leq 0.05$ level for treatment at a dose level to be considered effective. A step-down, multiple-comparison procedure was used to compare the efficacy of each Avanafil dose group with placebo as previously described.

In order to test for efficacy for the three dose groups, the Applicant used a step-down procedure, starting with the 200 mg. In this procedure, if the higher dose failed on one co-primary endpoint, no further testing occurred. In analysis of co-primary endpoints derived from the subject diaries (SEP 2 and SEP 3), only the observed data were employed. For the co-primary endpoint based on IIEF data, the last observation carried forward (LOCF) algorithm was used. The primary analyses of the two phase 3 studies (Study TA-301 and TA-302) are presented in the tables below:

Table 2: Mean Change in the Primary Efficacy Variables from Baseline to the End of Treatment Period – Study TA-301 Intent-to-Treat Population

	Placebo (N=155)	Avanafil 50 mg (N=154)	Avanafil 100 mg (N=157)	Avanafil 200 mg (N=156)
IIEF Domain Score				
Endpoint	15.3	18.1	20.9	22.2
Change from baseline**	2.9	5.4	8.3	9.5
Difference vs. placebo		2.6 (0.0014)	5.5 (<0.0001)	6.7 (<0.0001)
Vaginal Penetration (SEP2)				
Endpoint	53.8%	64.3%	73.9%	77.3%
Change from baseline**	7.1%	18.2%	27.2%	29.8%
Difference vs. placebo		11.1%(0.0009)	20.1%(<0.0001)	22.7%(0.0001)
Successful Intercourse (SEP3)				
Endpoint	27.0%	41.3%	57.1%	57.0%
Change from baseline**	14.1%	27.8%	43.4%	44.2%
Difference vs. placebo		13.8%(0.0002)	29.3%(<0.0001)	30.2%(0.0001)

*Table 2 adapted from Table 5 in the Statistical review dated April 9, 2012.
**Least-square estimate from ANCOVA model.

Table 3: Mean Change in the Primary Efficacy Variables from Baseline to the End of Treatment Period – Study TA-302 Intent-to-Treat Population

	Placebo (N=127)	Avanafil 100 mg (N=126)	Avanafil 200 mg (N=157)
IIEF Domain Score			
Endpoint	13.2	15.8	17.3
Change from baseline**	1.8	4.5	5.4
Difference vs. placebo		2.8(0.0017)	3.6(<0.0001)
Vaginal Penetration (SEP2)			
Endpoint	42.0%	54.0%	63.5%
Change from baseline**	7.5%	21.5%	25.9%
Difference vs. placebo		14.0%(0.0004)	18.4%(<0.0001)
Successful Intercourse (SEP3)			
Endpoint	20.5%	34.4%	40.0%
Change from baseline**	13.6%	28.7%	34.0%
Difference vs. placebo		15.2%(<0.0001)	20.4%(<0.0001)

*Table 3 adapted from Table 6 in the Statistical review dated April 9, 2012.
**Least-square estimate from ANCOVA model.

Dose selection of the 100 mg starting dose was discussed prior to and during the NDA review cycle. A detailed discussion of the rationale for the proposed initiating dose of 100 mg and the rationale for approval of the 200 mg dose is outlined in the CDTL review dated April 25, 2012. His rationale included the following, "The Sponsor provided evidence to support the rationale for the 200 mg dose by showing the need for a higher dose in several, clinically relevant sub-populations, such as subjects with diabetes, subjects ≥ 65 years, subjects with severe ED at baseline, and subjects with prolonged history of ED (duration ≥ 60 months)." The CDTL reviewer concluded that, "There is adequate rationale for all three avanafil doses."

Comment: I concur with the Medical Officer and CDTL that there is adequate rationale for all three proposed doses.

In his April 17, 2012, review, the Medical Officer concluded that, "The results showed that avanafil was effective in the treatment for ED as demonstrated by all three co-primary endpoints." The CDTL reviewer additionally stated that, "In three, randomized, double-blind, placebo-controlled studies (both Phase 3 studies TA-301 and TA-302, as well as the Phase 2 study TA-05), avanafil, at doses of 50 mg, 100 mg and 200 mg, demonstrated efficacy in the treatment of ED. The treatment effect is highly statistically significant compared to placebo and is clinically meaningful." (See review dated April 25, 2012)

Comment: I concur with the Medical Officer and CDTL that Study TA-301 and Study TA-302 each showed statistically improvement in the three co-primary endpoints with the three studied doses of Stendra (avanafil) compared to placebo. These results demonstrate acceptable efficacy at all three proposed doses (50 mg, 100 mg, and 200 mg).

Statistical review of the primary efficacy results for TA-301 and TA-302:
The statistical review for this NDA was primarily based on the two double-blind phase 3 studies, TA-301 and TA-302. In a review dated April 9, 2012, the statistical reviewer stated that, "Based on reviewer's analyses, the results support the efficacy of Avanafil 50 mg, 100 mg and 200 mg in the improvement of all three protocol specified co-primary endpoints. The treatment effects of Avanafil 100 mg and 200 mg on all three co-primary endpoints are statistically significantly better than Avanafil 50 mg. Although Avanafil 200 mg is not statistically more effective than Avanafil 100 mg, numerical improvement was seen in diabetic subjects. From a statistical perspective, all doses of Avanafil (50 mg, 100 mg and 200 mg) are effective in treating ED."

Comment: I also concur with the Statistical review team that the 50 mg, 100 mg, and 200 mg doses have demonstrated efficacy through Studies TA-301 and TA-302. Although efficacy results were obtained from the long-term extension study (TA-314), they were not reviewed by the clinical and statistical teams for efficacy claims because of the open-label study design.

The clinical review team also performed evaluation of two Phase 2 studies (TA-01 and TA-03), and subpopulation analyses by age, baseline ED severity, duration of erectile dysfunction and diabetes status. For all baseline ED subgroups and ED duration subgroups, treatment with avanafil resulted in a clinically relevant increases in the rates of successful intercourse and successful vaginal penetration. The magnitude of the treatment effects in these sub-group analyses appeared to be dose-related.

After evaluation of the overall results from the pivotal study that evaluated subjects with ED who had diabetes (TA-302), the Medical Officer stated that, "As observed, the magnitude of the treatment effect of avanafil on erectile function was numerically greater in subjects without diabetes than in subjects with diabetes, it is speculated whether or not these may be related to a function of the greater degree of ED severity at baseline in men with diabetes….. In both diabetics and non-diabetics, there was a dose-response relationship, with 200 mg being numerically better than 100 mg. The 200 mg dose provided clear numeric improvements in ED compared to the 100 mg dose in diabetics,

as well as in older, non-diabetic men, and in non-diabetic men with more severe or prolonged baseline ED. The improvement observed for the 200 mg dose over the 100 mg dose in other non-diabetic populations was numerically smaller."

(b) (4)

[redacted]

Comments:

1. *I concur that the data from pivotal study TA-302 support that Stendra treatment in subjects with diabetes results in improvement in erectile dysfunction and that the response appears to be a dose-response relationship.*
2. *In terms of* (b) (4) *claims, I do not concur with the Applicant that Stendra*

(b) (4)

[redacted]

Efficacy summary:

The main objective of the Applicant's NDA submission was to demonstrate that Stendra (avanafil) was effective in the treatment of erectile dysfunction. The Medical Officer summarized efficacy results in his April 17, 2012, review as follows, "Avanafil met all three co-primary endpoints at all three doses (50, 100, and 200 mg) studied in the general ED population, and at both doses (100, and 200 mg) studied in diabetic men with ED." In addition, with regard to the dose-response relationship, he concluded that, "The clinical efficacy of avanafil is dose-related. The benefit of the 100 mg dose over the 50 mg dose is clear. The benefit of the 200 mg dose over the 100 mg dose is less clear compared to the 100 mg over the 50 mg. Nonetheless, in diabetics, the benefit of the 200 mg over the 100 mg is evident, and for non-diabetics the benefit of the 200 mg over the 100 mg is evident in the elderly (> 65 years), as well as in men with severe ED or a longer history of ED at baseline."

In his review dated, April 25, 2012, the Cross-Discipline Team Leader further concluded that, "Therefore, the doses proposed by the Sponsor (b) (4) [redacted]

[redacted] (50 mg, 100 mg and 200 mg) are considered scientifically and clinically justified. The 100 mg dose is an appropriate starting dose, with potential for increase to 200 mg [redacted], and potential to decrease dose to 50 mg [redacted] with tolerability issues."

Based on the submitted efficacy results from two adequate and well-controlled trials (Studies TA-301 and TA-302) for Stendra, it is reasonable to conclude that the proposed Applicant's product will be efficacious for the treatment of erectile dysfunction. Therefore, I concur with the recommendations of the clinical review team, statistical review team and Cross-Discipline Team Leader that there are no outstanding efficacy concerns for this new PDE5 inhibitor product.

8. Safety

The safety data for Stendra (avanafil) were primarily derived from the 23 clinical studies contained in the NDA submission: 1) the two pivotal phase 3 studies (Study TA-301 and TA-302) three supportive studies (TA-01, TA-03, and TA-05), the long-term (9-month) extension study (TA-314) and 17 phase 1 studies that included a thorough QT study (TA-140) and other drug-drug interaction studies (Studies TA-04, TA-011, TA-016, TA-017, TA-018 and TA-019). An additional phase 3 study (TA-303), which was a randomized, double-blind, placebo-controlled, parallel study in men with erectile dysfunction who had a radical prostatectomy, was submitted with the 120-safety update and reviewed solely for purposes of safety.

The safety database consists of a total of 1923 subjects exposed to at least one dose of Stendra. Of these subjects:

- 621 subjects received avanafil in phase 1 studies.
- 360 subjects received avanafil in phase 2 studies
- 942 subjects received avanafil in phase 3 studies
- 198 subjects received avanafil in Study TA-303 in subjects who had a radical prostatectomy and subsequently developed ED. TA-303 was evaluated solely for safety, but were not evaluated as part of the integrated double-blind cohort analyses
- 712 subjects received avanafil in the open-label extension study (TA-314)

Phase 3 cohort (TA-301 and TA-302):

A total of 549 of 1032 (53.2%) subjects in the integrated double-blind phase 3 cohort took two doses of study drug within 24 hours: 158 of the 291 (54.3%) subjects in the placebo group, 88 of the 160 (55.0%) subjects in the avanafil 50 mg group, 151 of the 288 (52.4%) subjects in the avanafil 100 mg group, and 152 of the 293 (51.9%) subjects in the avanafil 200 mg group.

Long-term extension study (TA-314):

Study TA-314 was an open-label extension study that enrolled subjects who had completed either Study TA-301 or TA-302 for an additional 40 weeks of treatment. All subjects were assigned to treatment with avanafil 100 mg. Subjects who were unable to tolerate treatment could request that their dose be reduced to 50 mg. Subjects who were able to tolerate treatment with 100 mg could request that their dose be increased to 200 mg.

A total of 712 subjects from Studies TA-301 or TA-302 (who received treatment during a 12-week double-blind period) were enrolled in TA-314 and followed for up to an additional 40 weeks of treatment time for a total of 52 treatment weeks. A total of 493 subjects were exposed to avanafil for ≥ 6 months (26 weeks) and 153 subjects were exposed to avanafil for ≥ 12 months (52 weeks). Overall, the mean total number of doses taken was 68.6: 47.5 doses for subjects who received avanafil 100 mg only during this study; 75.4 doses for subjects who received avanafil 100 mg and 200 mg during this study; and 58.2 doses for other subjects (i.e., subjects who received avanafil 100 mg and 50 mg and subjects who received all three doses of avanafil).

Comment: No other postmarketing surveillance data is available for review other than that provided in the database from the clinical trials performed to date.

The Medical Officer reviewed the total population exposure data in his review dated April 17, 2012, and stated that, "This reviewer believes that for NDA 202276, the total population exposure requirement is sufficient, including the long-term exposure."

Comment: I concur with the Medical Officer that the safety database was sufficient to support approval of Stendra.

Deaths, Serious Adverse Events and Discontinuations due to Adverse Events in the pivotal phase 3 studies (TA-301 and TA-302):

Deaths: One death occurred in the clinical trial safety database for Stendra in Study TA-301. This subject died from a self inflicted gunshot wound and was not considered by the Applicant or the Division to be related to the study drug.

Non-fatal Serious Adverse Events (SAE): In the double blind cohort (TA-301 and TA-302), a total of 17 subjects (1.6%) had an SAE. By treatment group, 3 subjects (1.0%) in the placebo group, 1 subject (0.6%) in the avanafil 50 mg group, 6 subjects (2.1%) in the avanafil 100 mg group, and 7 subjects (2.4%) in the avanafil 200 mg group. No specific SAE was reported by more than 1 subject in any treatment group. Neither the Applicant nor the Division considered any SAE to be caused by study drug.

Comment: In the April, 2012, CDTL review, two serious adverse events related to coronary artery disease occurred within 24 hours of taking avanafil. I agree with the CDTL that a relationship between avanafil use and these events cannot be excluded, but believe that the history of preexisting coronary artery disease in these subjects makes further interpretation difficult.

Discontinuations: In the double-blind cohort, a total of 22 subjects (2.1%) had an adverse event that resulted in study drug discontinuation: 5 subjects (1.7%) in the placebo group, 3 subjects (1.9%) in the avanafil 50 mg group, 8 subjects (2.8%) in the avanafil 100 mg group, and 6 subjects (2.0%) in the avanafil 200 mg group. No specific adverse event led to study drug discontinuation for more than 3 subjects in any treatment group.

Comment: The Medical Officer and CDTL reviewed narratives of the fatal and non-fatal serious adverse events and discontinuations and agreed that there were no events that raised new safety concern or imbalances that indicated new safety trends in the pivotal phase 3 safety database. I concur with their assessments.

Treatment Emergent Adverse Events (TEAEs)

The most frequent TEAEs were those known to be associated with PDE5 inhibitors. TEAEs in the 2 pivotal trials (TA-301 and TA-302) reported at a higher incidence in the active drug groups than placebo are shown below (as outlined by the CDTL in his April 25, 2012 review) and included:

- Headache (placebo, 1.4%; avanafil 50 mg, 4.4%; avanafil 100 mg, 5.9%; and avanafil 200 mg, 10.2%);
- Flushing (placebo, 0.0%; avanafil 50 mg, 3.8%; avanafil 100 mg, 4.2%; and avanafil 200 mg, 3.8%);
- Dyspepsia (placebo, 0.0%; avanafil 50 mg, 0.6%; avanafil 100 mg, 0.3%; and avanafil 200 mg, 1.4%), and
- Diarrhea (placebo, 0.0%; avanafil 50 mg, 0.6%; avanafil 100 mg, 0.3%; and avanafil 200 mg, 1.4%);
- Sinus congestion (placebo, 0.0%; avanafil 50 mg, 0.6%; avanafil 100 mg, 1.7%; and avanafil 200 mg, 0.3%), and
- Upper respiratory infection (placebo, 0.3%; avanafil 50 mg, 1.9%; avanafil 100 mg, 0.7%; and avanafil 200 mg, 0.3%).

The Medical Officer stated in his April, 17, 2012, review that most of the adverse events were mild or moderate in severity and that the distribution of common adverse events by maximum severity was similar across treatment groups. The noticeable TEAE in the Phase 3 double blind studies was headache occurring in the placebo, and avanafil 50 mg, 100 mg and 200 mg groups at incidences of 1.4% and 4.4%, 5.9% and 10.2%, respectively.

Comment: After review of the adverse event data from the two phase 3 studies (TA-301 and TA-302), the Medical Officer and CDTL concluded that the safety profile for Stendra was acceptable and appeared to be similar to other PDE 5 inhibitor products.

Vital Sign Findings

All PDE 5 inhibitor products cause vasodilation, and therefore may cause clinically significant decreases in blood pressure. The Medical Officer performed a focused

evaluation of abnormal increases and decreases in SBP and DBP in different subject cohorts including the double-blind cohort of 1150 subjects (obtained from Studies TA-05, TA-301 and TA-302) and the open-label cohort (Study TA-314). Data from these studies demonstrated that the BP decreases reported with the highest dose of Stendra (200 mg) was greater than those observed with the lowest Stendra dose (50 mg). All three Stendra doses (50 mg, 100 mg, 200 mg) resulted in decreases in BP that were generally greater than those observed with placebo.

Study TA-02 was designed to specifically evaluate the effect of Stendra on blood pressure. After a single dose of avanafil 200 mg, the greatest mean reduction in SBP and DBP over placebo were -4.8 and -5.3 mmHg, respectively; these changes were observed at approximately 4 hours after drug intake. The Medical Officer concluded in his April 17, 2012, review that, "The results from Study TA-02 demonstrate that like other PDE5 inhibitors, avanafil is associated with a transient decrease in blood pressure soon after dosing. Additional information relevant to blood pressure was also collected in other Phase 1 studies (either in extrinsic factor studies or in drug-drug interaction studies) did not showed unexpected effects of avanafil on blood pressure changes.

Comment: The Medical Officer and CDTL did not identify any new safety signals from the vital sign data for Stendra.

Laboratory Findings

The Medical Officer performed a focused evaluation of marked laboratory abnormalities in different subject cohorts including the double-blind cohort of 1150 subjects (obtained from Studies TA-05, TA-301 and TA-302) and the open-label cohort (Study TA-314). This safety evaluation included hematocrit, liver function testing and serum creatinine. In his April 17, 2012, review, the Medical Officer did not identify any significant shift summaries or meaningful changes in laboratory parameters and concluded that, "The numbers and percentages of subjects with abnormal laboratory measurements were low, and no meaningful differences among the treatment groups were reported."

Comment: The Medical Officer did not identify any new safety signals from the laboratory data for Stendra.

Clinically important findings from long-term study TA-314:

Study TA-314 was an open-label extension study that evaluated the long-term safety and tolerability of avanafil in subjects with mild to severe ED for an additional 40 weeks of treatment to capture a total of 52 weeks of total exposure. All 712 subjects were enrolled from the two pivotal phase 3 studies (TA-301 or TA-302). All subjects were initially assigned to treatment with 100 mg and during the study, subjects could have their dose up-titrated to 200 mg or down-titrated to 50 mg based on their individual responses to treatment. The mean duration of exposure to avanafil was 35.3 weeks, and the median duration of exposure was 38.1 weeks. In total, 493 subjects were exposed to avanafil for

≥ 6 months (26 weeks) and 153 subjects were exposed to avanafil for ≥ 12 months (52 weeks).

Of the 712 enrolled subjects, 492 subjects (69.1%) completed the study and 20 subjects (2.8%) discontinued because of an adverse event with 10 of these subjects having an adverse event resulting in discontinuation that was related to study drug. No subjects died in Study TA-314 and eleven subjects had an SAE. The SAE resulted in discontinuation of study drug for 6 subjects: 1 subject with acute psychosis, 1 subject with femoral artery occlusion, 1 subject with coronary artery disease, 1 subject with aortic valve stenosis, 1 subject with cervical vertebral fracture, and 1 subject with congestive cardiac failure.

A total of 275 subjects (38.7%) had an adverse event that was considered by the investigators related to study drug. The most frequently reported events included headache (5.6%), flushing (3.5%), nasopharyngitis (3.4%), nasal congestion (2.1%), upper respiratory tract infection (1.5%), influenza (1.5%), and back pain (1.5%). The Medical Officer commented that the incidence of adverse events, in general, was higher with avanafil 200 mg treatment compared to 100 mg treatment. In summary, the Medical Officer stated in his April 17, 2012, review that, "The common adverse event profile includes headache, flushing, nasal congestion, as well as dizziness, dyspepsia and nausea. The profile of common adverse events (in the long-term study) is similar to other marketed PDE 5 inhibitors.

Comment: I concur with the Medical Officer's conclusion that the long-term study adverse event profile appears similar to those that have been reported for other PDE 5 inhibitor products.

Clinically important safety findings from study TA-303:

Study TA-303 was a double-blind, randomized, parallel study that was conducted in men who had undergone radical prostatectomy and subsequently developed ED. This study was submitted with the 120-day safety update, and therefore, not considered for additional efficacy claims. For the majority of subjects in each treatment group, the duration of exposure was ≥ 12 weeks.

The mean age of subjects was 58.4 years and the majority of subjects were White (81.5%). Across all treatment groups, the erectile dysfunction severity at baseline was mild for 9.1% of subjects, moderate for 19.5% of subjects, and severe for 71.5% of subjects. The mean duration of erectile dysfunction was similar between the treatment groups. The majority of subjects had robotic surgical technique for their radical prostatectomy (80.5%). The Medical Officer concluded that the treatment groups were comparable with respect to demographic and baseline characteristics.

Of the 298 randomized subjects, 252 (84.6%) completed the study and 5 subjects (1.7%) discontinued because of an adverse event (3 subjects in the avanafil 100 mg group and 2

subjects in the avanafil 200 mg group). No subjects died or had an SAE in Study TA-303.

In his review dated April 25, 2012, the CDTL reviewed the adverse event data and commented that, "The profile of adverse events commonly reported in the Phase 3, 40-week, open-label extension study TA-314 was the same as in the 12-week, placebo-controlled, phase 3 studies, with slightly lower incidences."

Comment: I concur with the Medical Officer that there do not appear to be any new safety trends observed in the radical prostatectomy patient group treated with avanafil in TA-303.

Clinically important safety findings from supportive phase 1 and 2 studies:

Deaths: No deaths were reported in the phase 1 and 2 studies.

Non-fatal Serious Adverse Events (SAE): No subjects had an SAE in the supportive phase 2 studies and only one subject reported an SAE of pharyngolaryngeal pain in Study TA-02, which was diagnosed as a tonsillar abscess. This SAE was not considered by the investigators or the clinical review team to be drug-related.

Discontinuations: In the two phase 2 studies, one subject in Study TA-03 discontinued treatment because the partner of the subject became pregnant. In the phase 1 studies, one subject discontinued because of the SAE of pharyngolaryngeal pain described above. No other subjects discontinued study drug in the phase 1 program because of an adverse event.

Other Significant Safety Issues:

1. Avanafil nitrate interaction:

As there is a possibility of concomitant nitrate use with avanafil, information was needed to label the effects of nitrates on blood pressure in patients taking avanafil. Study TA-04 was performed using a sublingual dose of glyceryl trinitrate in subjects receiving oral avanafil, sildenafil, and placebo in a single center, double blind, randomized, 3-way crossover study in healthy male subjects aged 30 to 60 years. Subjects were divided into 5 study groups, with the study groups differing in the time interval (0.5 [n=23], 1 [n=20], 4 [n=19], 8 [n=13], and 12 [n=13] hrs) between treatment with avanafil (200 mg), sildenafil (100 mg), or placebo and glyceryl trinitrate (0.4 mg) administration.

A statistically significant interaction between avanafil and glyceryl trinitrate was observed at the 0.5 hour time point for blood pressure and pulse rate. However, the percentage of subjects with clinically significant BP drops (e.g., >30 mmHg) was actually 38-39% for avanafil compared to 4-10% for placebo in the first hr after dosing). In addition, orthostatic hypotension adverse events were reported at approximately twice the rate in avanafil subjects when compared to placebo treated subjects.

In his CDTL review dated April 25, 2012, the CDTL concluded that, "Avanafil, like all other PDE5 inhibitors has a significant pharmacodynamic interaction with nitroglycerin and these drugs should not be taken together. The timepoint at which nitroglycerin can be safely administered after a dose of avanafil was not clearly defined in this study; therefore, based upon an abundance of caution, the label should recommend 12 hours, and even then, with careful monitoring."

Comment: I concur with the CDTL's conclusions and agree with his labeling recommendations.

2. Alcohol interaction:

As there is a possibility of an additive hypotensive effects of PDE5 inhibitor products, such as avanafil with alcohol, safety data was requested to evaluate the interaction. Study TA-015 evaluated the pharmacodynamic effects of concomitant administration of 200 mg avanafil and alcohol (0.5 gm of absolute ethanol/kg body weight) in a Phase 1, single center, double-blind, randomized, placebo-controlled, three-period, three-way crossover study in 15 young (age 22 – 44) male subjects. Data from Study TA-015 showed decreases in both mean systolic and mean diastolic blood pressure with concomitant avanafil and alcohol use.

In his CDTL review dated April 25, 2012, the CDTL concluded that, "Avanafil, like all other PDE5 inhibitors, has an interaction with alcohol. The avanafil label should advise against excessive intake of alcohol (e.g., > 3 glasses of wine, or 3 shots of whisky) in combination with avanafil use.

Comment: Study TA-015 was performed in a relatively younger population than that likely to use this product in the US. It is also likely that the blood pressure decreases in this older population could be significantly more than what is seen in this study, and that those decreases are likely to be clinically relevant. Based on the decreased blood pressure results seen in the younger population in this study and experience with other PDE5 inhibitors having hypotension with concomitant alcohol use, the interaction between alcohol and avanafil should be labeled as a warning.

3. Safety studies on spermatogenesis:

Animal studies of avanafil showed adverse effects on spermatogenesis and fertility. The Applicant conducted two studies (TA-014 and TA-021) that included limited evaluation of the effects of avanafil on human sperm as described below:

- Study TA-014 was a single dose (200 mg), non-randomized, open-label, 2-cohort study in healthy male subjects, which assessed the effect of age on the pharmacokinetics of avanafil. The cohorts included younger men (43 years of age or less) and elderly men (aged 65 -80). Avanafil semen exposure and the effect of avanafil in subjects 19-43 years of age were evaluated. Among the Applicant's conclusions for Study TA-014 was that, "Mean sperm motility remained within

the reference range and did not change by >20% from baseline. There was no acute effect on morphological normal forms, sperm count, sperm concentrations and forward progress."

- Study TA-021 was a single dose (200 mg), randomized, double-blind, placebo-controlled, 2-period crossover study which assessed the effect of a single dose of avanafil on sperm function in healthy male subjects. Among the Applicant's conclusions for Study TA-021 was that, "Mean values for all semen parameters (sperm concentration, sperm motility, forward progression, total sperm count, sperm morphology, and total motile sperm count) were within normal limits at the Day 1 post-dose assessment for avanafil treatment group."

The Medical Officer concluded in his April 17, 2012, review that, "Both Studies TA-014 and TA-021 were single-dose studies, and the efforts from longer term use are unknown at this moment." The CDTL also raised concerns that the "Potential adverse effects of avanafil on human sperm after longer-term use are currently unknown." (See CDTL review dated April 25, 2012.

Comment: Although in single-dose human sperm studies, there were no effects of avanafil on sperm motility or morphology, there were negative effects in animal studies. Therefore, I concur that a multiple dose study of avanafil on sperm is an outstanding safety issue that should be addressed as a postmarketing requirement. I also concur that labeling should state that the effect of avanafil on human sperm is unknown until the results of this postmarketing study are available for review.

4. Ophthalmology adverse events:

No dedicated vision study was conducted to evaluate avanafil's effects on vision. Effects of avanafil on color discrimination and with use of warfarin were evaluated and included as part of limited vision investigations in two phase 1 studies, HP-01 and TA-016 as described below:

- Study HP-01 was a double-blind, single-ascending dose study of the safety, tolerability and pharmacokinetics of avanafil in healthy male volunteers. The study included a test of color discrimination following placebo or avanafil single doses of 12.5 mg to 800 mg prior to and after drug administration
- Study TA-016 was a Phase 1, single-center, double-blind, randomized, placebo-controlled, 2-way crossover study to assess the potential interaction of avanafil on the pharmacokinetics and pharmacodynamics of warfarin in healthy male volunteers. Following the warfarin dose, PK and PD sampling was taken over a period of 7 days. Potential for color vision impairment with avanafil was part of the PD assessment.

The Medical Officer and CDTL evaluated the visual safety data from these two studies and concluded that the data represented only limited vision safety data because of the design of these studies. The Medical Officer stated that, "This Reviewer believes that a special designed, dedicated study to evaluate effects of avanafil on vision, including but not limited to visual acuity, intraocular pressure, pupillometry and color vision

discrimination, should be conducted by the Sponsor as a postmarketing requirement (PMR)."

Specifically, with respect to Study TA-016, the CDTL concluded in his review dated April 25, 2012, that, "The purpose of this study was to compare the effects on color vision beween warfarin + avanafil and warfarin + placebo. From this design, no conclusions can be reached as to whether avanafil itself has effects on color vision. Nevertheless, a difference was observed between avanafil and placebo in total error score and square root of the total error score (when an outlier was excluded). To resolve the potential effect of avanafil on vision, the Sponsor has agreed to conduct a special designed, dedicated postmarketing vision study to evaluated the effects of avanafil on, but not limited to, visual acuity, intraocular pressure, pupillometry and color vision discrimination"

Comment: Men taking PDE 5 inhibitors have reported sudden losses of vision. Therefore, I concur that lack of a dedicated vision study for avanafil is an outstanding safety issue.

Safety summary:

The safety database for Stendra (avanafil) tablets supports that there is no evidence to suggest that the safety profile of avanafil would be different from other approved PDE5 inhibitors in its class. The most common adverse events in the clinical trials (seen in >2% of subjects and more frequently than seen in placebo) were headache, flushing, nasopharyngitis, and back pain. The adverse events of sudden visual loss and sudden hearing loss are labeled for all of the PDE5 inhibitors. There were no events of this nature in the avanafil treated subjects, although one episode of sudden hearing loss occurred in a subject who received placebo.

In summary, the Medical Officer concluded the following on the safety database for Stendra in his review dated April 17, 2012, "The exposure of avanafil to patients and other subjects including the long-term exposure complied with ICH standards. Overall, the safety and tolerability profile of avanafil appear acceptable. Common adverse effects mainly consist of AE profile of other PDE5 inhibitors."

The Cross-Discipline Team Leader (CDTL) concurred with the primary Medical Officer's recommendation that the safety profile of Stendra was acceptable in his CDTL review (dated April 25, 2012) and stated, "There are no deficiencies in the avanafil efficacy and safety data that preclude approval."

The clinical review team, however, determined that there were two safety issues identified that were not sufficiently addressed after review of the NDA safety database. These remaining safety issues included: 1) the effects of avanafil use on spermatogenesis and 2) the effect of avanafil use on visual changes. The clinical team agreed that these two safety issues could be evaluated through postmarketing requirements.

I concur with the recommendations of the primary Medical Officer and CDTL that there are no remaining safety concerns that preclude approval of this NDA. The clinical review team also determined that two identified safety issues (alteration of spermatogenesis with avanafil use and visual changes with avanafil use) could be evaluated as postmarketing requirements. I concur that these issues need to be further assessed through postmarketing requirements. Additional details on these postmarketing requirements are briefly outlined in section 12 below.

9. Advisory Committee Meeting

The first PDE5 inhibitor, sildenafil, was approved in 1995 for treatment of erectile dysfunction. Since then, other PDE5 inhibitor products have been approved and used in clinical practice. The safety issues associated with PDE5 inhibitor therapies are well known and can be adequately labeled. In addition, no new safety concerns were identified for avanafil. Therefore, no Advisory Committee was convened.

10. Pediatrics

The Applicant requested a full waiver of the requirement to conduct assessments of avanafil tablets in pediatric patients. The Division agreed with the Applicant that a full waiver was acceptable because studies would be highly impractical to conduct and because the disease/condition does not exist in normal children.

The Pediatric Review Committee (PeRC) agreed with the Division that "PREA does not apply" and granted a full pediatric waiver for Stendra.

11. Other Relevant Regulatory Issues

Division of Medical Policy Programs (DMPP):

DMPP reviewed the Patient Package Insert (PPI) on April 17, 2012, and found it to be acceptable with several recommended changes. The Division discussed several of the recommendations with DMPP, and after minor editing, the agreed to recommendations were implemented.

Office of Prescription Drug Promotion (OPDP):

OPDP reviewed the Prescribing Information and the Patient Package Insert. OPDP completed their review of Prescribing Information on April 18, 2012. Their recommendations were implemented.

Office of Scientific Investigations (OSI):

OSI conducted inspections of three clinical sites (Drs. Surowitz, Cook and Rosen) and the Applicant (Vivus, Inc.) in support of this NDA. After these inspections were

conducted and assessed by OSI, the Clinical Inspection Summary stated that, "Overall, the studies at these three clinical sites appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication." (See OSI Clinical Inspection Summary dated March 16, 2012)

Division of Medication Error Prevention and Analysis (DMEPA):

The DMEPA review team provided a final review on April 26, 2012 of container labels, Physician Sample labels, Physician Sample, Carton labeling, and packaging for Stendra (Avanafil) NDA 202276 for areas of vulnerability that could lead to medication errors. DMEPA's recommendations were implemented.

DMEPA also assessed the proposed tradename "Stendra" on April 23, 2012, and found it acceptable.

Financial Disclosures**:**

The clinical review team did not identify any issues related to financial disclosures for these studies (See clinical review dated April 17, 2012).

Study Endpoints and Labeling Development Team (SEALD)**:**

The SEALD review team reviewed the label in a review dated April 25, 2012 and provided recommendations. These recommendations were implemented.

12. Labeling

Labeling negotiations are complete. Labeling for Stendra (avanafil) was acceptable to the review teams and also consistent with labeling of previously approved PDE5 products for treatment of erectile dysfunction. Labeling was also evaluated by the following groups:

- Office of Medical Policy Programs (DMPP) reviewed the label and the Medication Guide and their recommendations were considered during labeling negotiations with the Applicant.
- Office of Prescription Drug Promotion (OPDP) reviewed the label and Medication Guide and their recommendations were considered during labeling negotiations with the Applicant.

Labeling was reviewed by the Study Endpoints and Label Development (SEALD) Team. An edited version of the label was sent to the Applicant. The Applicant accepted the requested edits from SEALD. No additional labeling review by SEALD was required.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the Cross-Discipline Team Leader, Medical Officer, and the Clinical Pharmacology, Pharmacology/Toxicology, CMC, and Statistical review teams that the Stendra (avanafil) tablet application can receive an Approval action.

Risk Benefit Assessment:

Two adequately controlled trials (TA-301 and TA-302) using accepted endpoints have demonstrated that Stendra tablets were effective in the treatment of erectile dysfunction. The results from both trials were consistently statistically significant, and efficacy has been demonstrated in the target population.

No new safety concerns were identified in clinical trials with Stendra tablets. Adverse findings reported in the safety database appeared to be qualitatively and quantitatively similar to those reported with those of other drugs in its class (PDE5 inhibitors). The most common adverse events (seen in >2% of subjects and more frequently than seen in placebo) were headache, flushing, nasopharyngitis, and back pain, which are similar to those seen with other PDE5 inhibitor products. The adverse events of sudden visual loss and sudden hearing loss are labeled for all of the PDE5 inhibitors and will also be labeled for Stendra. None of these events were reported in the trials for Stendra, although one episode of loss of color vision occurred in a subject receiving Stendra.

The risk/benefit assessment favors approval of Stendra (avanafil) for the treatment of erectile dysfunction.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

- The review teams determined that a REMS was not necessary for this product.
- The review teams recommended the following two postmarketing requirements (PMRs):
    - A randomized, double-blind, placebo-controlled, parallel group, multicenter trial of the effect of avanafil on sperm in healthy adult males and adult males with mild erectile dysfunction
    - A double-blind, randomized, placebo-controlled, single-dose trial to assess the effects of avanafil on multiple parameters of vision, including, but not limited to visual acuity, intraocular pressure, pupilometry, and color vision discrimination, in healthy male subjects.

The Applicant agreed to perform these two PMRs and proposed acceptable milestones for completion of these trials.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AUDREY L GASSMAN
04/26/2012